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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): MORRIS, et al. Docket No.: 134.02120120

Patent No.: 6,945,969

Issued: September 20, 2005

Title: CATHETER FOR TARGET SPECIFIC DRUG DELIVERY

Attention Certificate of Correction Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

We are transmitting the following documents along with this Transmittal Sheet (which is submitted in triplicate):

X An itemized return postcard.
___ A Petition for Extension of Time for __ month(s) and a check in the amount of $___ for the required fee.
___ A check in the amount of $___, for __.
___ A certified copy of a __ application, Serial No. __, filed _____, the right of priority of which is claimed under 35 U.S.C. §119.
X Other: A Request for Certificate of Correction (1 pg); a Certificate of Correction (1 pg); and a copy of the text noting corrections (in duplicate) (6 pgs).
___ Amendment ___ No Additional fee is required. ___ The fee has been calculated as shown:

Fee Calculation for Claims Pending After Amendment					
	Pending Claims after Amendment (1)	Claims Paid for Earlier (2)	Number of Additional Claims (1-2)	Cost per Additional Claim	Additional Fees Required
Total Claims				x $50 =	
Independent Claims				x $200 =	
One or More New Multiple Dependent Claims Presented? If Yes, Add $360 Here →					
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Please consider this a PETITION FOR EXTENSION OF TIME for a sufficient number of months to enter these papers and please charge any additional fees or credit overpayment to Deposit Account No. 13-4895. Triplicate copies of this sheet are enclosed.

MUETING, RAASCH & GEBHARDT, P.A.
Customer Number: 26813

By: KWR
Name: Kevin W. Raasch
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CERTIFICATE UNDER 37 CFR §1.10::
"Express Mail" mailing label number: EV 201876236 US Date of Deposit: April 25, 2006
I hereby certify that the Transmittal Letter and the paper(s) and/or fee(s), as described hereinabove, are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR §1.10 on the date indicated above and is addressed to: Attention Certificate of Correction Branch, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

By: Deb Schurmann
Name: Deb Schurmann

(LARGE ENTITY TRANSMITTAL UNDER RULE 1.10)

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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One or More New Multiple Dependent Claims Presented? If Yes, Add $360 Here →					
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Customer Number: 26813

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"Express Mail" mailing label number: EV 201876236 US Date of Deposit: April 25, 2006
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By: Deb Schurmann
Name: Deb Schurmann

MAY 1 2006

(LARGE ENTITY TRANSMITTAL UNDER RULE 1.10)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): MORRIS et al.
Patent No.: 6,945,969
Issued: September 20, 2005

For: CATHETER FOR TARGET SPECIFIC DRUG DELIVERY

REQUEST FOR CERTIFICATE OF CORRECTION

Attention Certificate of Correction Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

A Certificate of Correction is requested to be issued correcting printing errors appearing in the above-identified United States patent. Two copies of the text noting the corrections for the Certificate are enclosed. Since none of the errors listed are due to Applicants' mistake, no fee is necessary for the Certificate. The corrections in the proposed Certificate of Correction do not involve such changes in the patent as would constitute new matter or would require reexamination.

Please mail the printed Certificate of Correction to the undersigned attorney.

CERTIFICATE UNDER 37 C.F.R. 1.10:

The undersigned hereby certifies that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR §1.10 on the date indicated below and is addressed to Attention Certificate of Correction Branch, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Deb Schurmann
Name: Deb Schurmann
"Express Mail" mailing label number:
EV 201876236 US
Date of Deposit: April 25, 2006

25 APRIL 2006
Date

Respectfully submitted
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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO.: 6,945,969
DATED: September 20, 2005
INVENTOR(S): Morris et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In column 8, line 46, please delete "described-in" and replace with -described in-.

In column 10, line 22, please delete "diff-users" and replace with -diffusers-.

In column 10, line 44, please delete "diff-users" and replace with -diffusers-.

In column 11, line 41, please delete "segment each," and replace with -segment, each-.

In column 12, line 33, please delete "delivery, segment" and replace with -delivery segment-.

MAILING ADDRESS OF SENDER:

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P.O. BOX 581415
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Customer Number 26813

PATENT NO. 6,945,969

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the catheter **22** joined by connector **50**. This construction provides additional benefits. For example, having the restrictor **90** upstream of the connector **50** acts as a pre-filter, and thus removes any particulates prior to connector **50**. This pre-filter function reduces particulates to the restrictors **70** and **70'** downstream of connector **50**, thus reducing the potential for different pressure drops and flow rates through the restrictors **70** and **70'** downstream of connector **50**, and ultimately the flow rate of the delivered drug through the diffusers or delivery segments **60** at the distal ends. In addition, this embodiment eliminates the possibility for incorrect insertion of a catheter where only one restrictor is downstream of connector, and one restrictor is upstream of connector **50**, and one leg **80** or **80'** not having a restrictor.

FIG. **5B** shows the same structure as FIG. **4B**, except that in this other embodiment of the present invention, a restrictor **90** is placed between proximal end **24** and the first connector **50** downstream of proximal end **24**, to deliver a drug to more than two targeted patient sites.

In accordance with the embodiments shown in FIGS. **4A**, **4B**, **5A**, and **5B**, the drug fluid is pushing through many small pores of the drug delivery segment **60**, and restrictors **70**, **70'** and **90** are of substantially equal flow resistance, and thus the delivered drug fluid follows a tortuous path. In these embodiments, the sum of the resistance to flow through multiple catheter distal ends is preferably equal so that equal flow is through the multiple catheter distal ends is obtained. The structures described above and shown in FIGS. **4A**, **4B**, **5A**, and **5B** provide substantially equal flow through multiple catheter distal ends. Further discussion about the drug delivery segment (i.e. diffuser) and the fluid restrictor is set forth below.

Fluid Diffuser—Fluid modeling reveals that distribution of fluid flow will occur with multiple small holes in simple silicone or polyurethane catheters. The diffuser, i.e., the drug delivery segment **60** shown in FIGS. **4A**, **4B**, **5A** and **5B**, can comprise any suitable structure. For example, the diffuser can comprise material having laser drilled holes or tubes having 0.001–0.005 inches (i.e., 0.0025–0.0127 cm) diameter, and about 20–100 holes per diffuser. In one embodiment, the most distal of forty holes having 0.005 inches (0.0127 cm) in diameter should have 76% of the flow compared to the most proximal hole (total flow 1 microliters/minute). For holes that are 0.001 inches (0.0025 cm) in diameter, the distal hole should have 99.95% of the flow compared to the proximal hole. In addition, many porous materials such as sintered metal, sintered polyethylene, or porous PTFE (i.e., Teflon) have diffuser capability. Thus, these structures are good diffusers at flow rates of about 1 microliter/minute to about 20 microliters/minute. For the diffuser material, a permeability constant of less than about 30,000 and a bubble point of less than about 10 psi is preferred.

As previously noted, the drug delivery segment can be made of any light-weight, high tensile strength material, e.g., tungsten, titanium or tantalum. Further, the drug delivery segment can be made of any suitable radiopaque material (e.g., tantalum, tungsten, titanium, gold, platinum, iridium, silver, nickel, and alloys thereof).

Suitable radiopaque material can be placed in any suitable portion of the medical catheter of the present invention, and is not limited to the drug delivery segment. Thus, the medical catheter of the present invention may include at least one portion comprising a radiopaque material from the group consisting of tantalum, tungsten, titanium, gold, platinum, iridium, silver, nickel and alloys thereof. Incoporation of a portion or marker, such as a band or bead, having radiopaque material can enable medical personnel to identify the location of the cathether and drug delivery segment within a patient, via X-ray, magnetic resonance imaging (MRI), and/or computerized axial tomography (CAT scan).

FIG. **6** is a cross section view of one preferred embodiment of a drug delivery segment (i.e. diffuser) **60** of the present invention taken from lumen distal end **39** of lumen **38** as shown in FIG. **7**. The drug delivery segment is implantable in a patient for long periods of time (i.e., exceeding more than 24 hours), and is particularly useful for implantable drug delivery devices and systems to treat chronic disorders. The drug delivery segment described herein prevents soft tissue from entering the tubes and blocking flow of the fluid from the drug delivery segment to the target site within a patient. The drug delivery segment **60** has an inside surface **120** and an outside surface **130**. In preferred embodiment, drug delivery segment has a longitudinal length of about 0.1–1.0 cm, and more preferably about 0.5 cm. In a preferred embodiment, the inside diameter of diffuser **60** is about 0.032 inches (0.0812 cm), and the outside diameter of diffuser **60** is about 0.064 inches (0.1625 cm). In this preferred embodiment, tubes **101** through **110** extend radially from the inside diameter of diffuser **60** to the outside diameter of diffuser **60**. In this embodiment, the length of the tubes **101** through **110** is about 0.016 inches (0.0406 cm). Preferably, the ratio of tube length to tube diameter of tubes **101** through **110** is about 5–25, and more preferably about 5.0. A benefit of the ratio of 5–25 of tube length to tube diameter is that flow resistance is provided, thereby permitting more equal flow between the most distal tube and the most proximal tube and thus assisting in the diffuser function. One way to obtain this tube structure is to use a laser or ion beam to drill tubes **101** through **110**. In one preferred embodiment, tubes **101** through **110** have substantially the same diameter.

As shown in FIG. **6**, tubes **110** can be tapered as they extend from the outside diameter of diffuser **60** to the inside diameter of diffuser **60**. Lumen **38** extends along the longitudinal axis of Q-Q of diffuser **60**. In a preferred embodiment, all of the tubes **101** through **110** (shown in FIG. **7**) have the same shape as they extend from the outside diameter of diffuser **60** to the inside diameter of diffuser **60**. While tubes **110** are shown as being tapered in FIG. **6**, they can also be non-tapered, or can have tapered and non-tapered sections.

As previously described in connection with FIG. **3B**, the opening defined by the distal end of the medical catheter can be a side opening. When the opening defined by the distal end of the catheter is a side opening, the drug delivery segment can cover the opening. In this alternative embodiment, the drug delivery segment does not define a lumen along its longitudinal axis, but still has tubes that extend radially from the outside surface of the drug delivery segment to the inside surface of the drug delivery segment, wherein the ratio of the length of the tubes to the diameter of the tubes is about 5–25. Further, any pattern of tubes can be used in connection with the present invention, including but not limited to, a pattern corresponding to the shape and/or location of an intended target site within a patient, e.g., a tumor.

FIG. **7** is a side view of one preferred embodiment of the drug delivery segment (i.e. diffuser) **60** of the present invention. In a preferred embodiment, the diffuser **60** comprises at least one row **100** parallel to the longitudinal axis Q-Q of diffuser **60**. In the embodiment shown in FIG. **7**, there are four rows **100** of tubes **101** through **110** extending along an axis parallel to the longitudinal axis Q-Q of

diff-user **60**. In this preferred embodiment, there are ten tubes per row **100**. Preferably, the tubes in each row are equally spaced from each adjacent tube in the same row **100**. As shown in FIG. **7**, tube **101** is the most proximal hole, and tube **110** is the most distal tube, and tube **105** is the middle-tube. As shown in FIGS. **6** and **7**, each row is about 90 degrees from each adjacent row along the outside diameter of diffuser **60** (as FIG. **7** is a side view, only three rows **100** of tubes **101** through **110** are shown). In FIG. **7**, the distance from the most proximal tube **101** to the most distal tube **110** is identified as distance "a", and the distance from the middle tube **105** to about the mid-point of catheter tip **34** is identified as distance "b". In a preferred embodiment, the distance from the most proximal tube **101** to the most distal tube **110** is about 5.5 millimeters, and the distance from middle-tube **105** to about the mid-point of catheter tip **34** is about 5.0 millimeters.

Those of skill in the art will recognize that the above preferred embodiment can be modified without departing from the scope of the present invention. For example, eight (8) rows can be used instead of four (4) rows, wherein each row is about 45 degrees from each adjacent row along the outside surface **130** of the drug delivery segment **60**. Each of the eight rows can have ten (10) tubes **101** through **110**, for a total of eighty (80) tubes.

The key factors in obtaining relatively equal flow through each of the tubes **101** through **110**, are as follows: (1) tube length relative to tube diameter; (2) number of tubes; and (3) an internal diameter of the diffuser **60** that is relatively large enough to provide fluid to the most distal tube **110**. Those of skill in the art will readily recognize how to vary these factors as may be desired for a given flow rate.

The above described embodiment is particularly useful for implantable medical catheters wherein the drug delivery segment is implantable for more than twenty-four hours to provide fluid containing a therapeutic drug to a target site in a patient at flow rates of about 2 microliters/hour to 10 microliters/minute.

Fluid Restrictor—To balance the flow into each hemisphere of the patient's brain, resistance to fluid flow in each leg of the catheter must be significant compared to the resistance at the tissue interface. If the restrictor creates a pressure drop of about 2–10 psi for a flow rate of about 10 microliters/minute, variation in interstitial pressure (less than 0.5 psi) will not create an imbalance of flow in the two catheter legs for a desired flow rate of about 1–10 microliters/minute. For this pressure drop, the material for the restrictor must be very tortuous and have a significant length (i.e., thickness). For the restrictor material, a permeability constant of less than about 5,000 and a bubble point of less than about 10 psi is preferred. Since the restrictor is separated from the diffuser in this embodiment, the dimensions and materials are not limited to those typically considered acceptable for intraparenchymal implant. Acceptable materials for restrictors given the larger lengths possible outside the brain are sintered porous metals, and sintered and/or porous polymers. Methods of manufacture and materials for the restrictors of the present invention include, but are not limited to, thin sheet filter (e.g., polyethersulfone or polypropylene, from Pall Corporation (East Hills, N.Y.)), polycarbonate membrane (from Osmonics, Inc. (Minnetonka, Minn.)), polyvinylidine fluoride from Millipore Corporation (Bedford, Mass.)), depth filters from sintered metal (from Mott, Inc. (Farmington, Conn.)), sintered polyethylene (from Porex Surgical (College Park)), sintered glass (from Robu Glasfilter-Gerate GmbH (Hattert, Germany)), orifice sapphire, and/or capillary tubes. Preferably, the restrictor is a depth filter since it does not have disadvantages that the other materials may have. Sheet membranes have a disadvantage in that they have very small pores that may be prone to clogging and require a high pressure to pass air through the wet membrane (i.e., bubble point). Orifice-type restrictors have the disadvantage of pressure drop that is extremely sensitive to diameter, thereby making it difficult and expensive to match two restrictors of this type to achieve substantially equal flow.

The restrictor should provide a large pressure drop. The pressure drop can be expressed by Darcy's Law. Darcy's Law is as follows:

$$K = \frac{-F\mu T}{A \cdot \text{delta P}}$$

where K=permeability constant
F=flow rate
μ=viscosity for the fluid
T=thickness of porous path
A=surface area
delta P=pressure delta

The conflicting requirements of the large surface area for a diffuser and a large pressure drop for the restrictor can be met by having separate structure for each of these functions.

Separating the restrictors from the diffusers, and placing the restrictors up stream of the diffusers results in the resistance to flow at the distal ends to be insignificant to the overall resistance to flow, and the fluid flow through multiple catheters is substantially equal.

An example is that for a "Y" catheter, if the resistance to flow through a first diffuser has a relative value of 1, and the resistance to flow through a second diffuser has a relative value of 2, then twice as much flow will go through the first diffuser.

On the other hand, if restrictors with a relative resistance value of 100 are placed up stream of the first and second diffusers, so that the overall resistance to flow through the first diffuser has a relative value of 101, and the overall resistance to flow through a second diffuser has a relative value of 102, then the flow through the first and second diffusers will be substantially equal. Equal restriction of fluid flow through each leg is the key to substantially equal fluid flow through each leg.

The features provided by this embodiment include:

1. Separate diffuser and restrictor features for bilateral intraparenchymal drug delivery catheter.
2. Use of simple diffusers that have insufficient tortuosity of the porous structure to make acceptable restrictors.
3. Use of multiple small holes (less than 0.005 inches in diameter; created with a laser) as a fluid diffuser.
4. Location of catheter restrictor at proximal end (not distal) of catheter to provide greater device flexibility, i.e., reduce the number of joint, bonds, components for distal catheter segment.
5. Capability to control flow in the brain catheter with changes in catheter design/materials not directly implanted in the brain tissues.

Thus, the present invention provides for multiple catheter ends for drug delivery. More specifically, the present invention provides for multiple catheter ends, e.g. at least two, into the brain of patient, and even more specifically, into the two different hemispheres of the brain, with each catheter end supplied with therapeutic drugs by the same pump, and with the fluid flow of the therapeutic agent being substantially equal between the two catheter ends.

The present invention also provides a catheter to diffuse a therapeutic agent over a large surface area than from a single point source. The benefits of this structure is that it decreases the fluid flux and reduces the change of damaging patient tissue. In order for equal or near equal bilateral drug

delivery to occur, two catheters are required. It is usually desirable to have equal flow in both catheters to deliver equal amounts of drug to both brain hemispheres.

The present invention can be used for many drug delivery applications, including but not limited to intraparenchymal tissue delivery, intrathecal drug delivery, and intra-cerebral ventricular (ICV) drug delivery.

Many modifications and variations may be made in the techniques and structures described and illustrated herein without departing from the spirit and scope of the present invention. For example, the present invention can be used to infuse a cytostatic agent into a malignant mass located in a variety of places in the body, or infuse a nerve growth factor into the intrathecal space of the spinal column, or to treat Alzheimer's disease by infusing indomethacin or other drug into a patient's hippocampus. Accordingly, the techniques and structures described and illustrated herein should be understood to be illustrative only and not limiting upon the scope of the present invention.

We claim:

1. A method for delivering a therapeutic drug comprising:

forming a drug delivery segment having a longitudinal axis, the drug delivery segment having an outside surface and an inside surface,

forming tubes in the drug delivery segment, each tube having a diameter and a length that extends radially from the inside surface of the drug delivery segment to the outside surface of the drug delivery segment, and where a ratio of the length of the tubes to the diameter of the tubes is about 5–25;

providing a therapeutic drug to the drug delivery segment for more than 24 hours from an intraparenchymal catheter; and

distributing the therapeutic drug in approximately equal amounts through the tubes defined in the drug delivery segment.

2. A method for delivering a therapeutic drug comprising:

forming a drug delivery segment having a longitudinal axis, the drug delivery segment having an outside surface and an inside surface,

forming tubes in the drug delivery segment, each tube having a diameter and a length that extends radially from the inside surface of the drug delivery segment to the outside surface of the drug delivery segment, and where a ratio of the length of the tubes to the diameter of the tubes is about 5–25;

providing a therapeutic drug to the drug delivery segment for more than 24 hours; and distributing the therapeutic drug in approximately equal amounts through the tubes defined in the drug delivery segment to the brain of a patient.

3. A method for delivering a therapeutic drug comprising:

forming a drug delivery segment having a longitudinal axis, the drug delivery segment having an outside surface and an inside surface,

forming tubes in the drug delivery segment, each tube having a diameter and a length that extends radially from the inside surface of the drug delivery segment to the outside surface of the drug delivery segment, and where a ratio of the length of the tubes to the diameter of the tubes is about 5–25;

providing a therapeutic drug to the drug delivery segment for more than 24 hours from an intrathecal catheter; and

distributing the therapeutic drug in approximately equal amounts through the tubes defined in the drug delivery segment.

4. A method for delivering a therapeutic drug comprising:

forming a drug delivery segment having a longitudinal axis, the drug delivery segment having an outside surface and an inside surface,

forming tubes in the drug delivery segment, each tube having a diameter and a length that extends radially from the inside surface of the drug delivery segment to the outside surface of the drug delivery segment, and where a ratio of the length of the tubes to the diameter of the tubes is about 5–25;

providing a therapeutic drug to the drug delivery segment for more than 24 hours from an intracerebral ventricular catheter; and

distributing the therapeutic drug in approximately equal amounts through the tubes defined in the drug delivery segment.

5. A method for delivering a therapeutic drug comprising:

forming a drug delivery segment having a longitudinal axis, the drug delivery segment having an outside surface and an inside surface,

forming tubes in the drug delivery segment, each tube having a diameter and a length that extends radially from the inside surface of the drug delivery segment to the outside surface of the drug delivery segment, and where a ratio of the length of the tubes to the diameter of the tubes is about 5–25;

providing a therapeutic drug to the drug delivery segment for more than 24 hours from a catheter; and

distributing the therapeutic drug into a liquid filled space within a patient in approximately equal amounts through the tubes defined in the drug delivery segment.

6. A method for delivering a therapeutic drug comprising:

forming a drug delivery segment having a longitudinal axis, the drug delivery segment having an outside surface and an inside surface,

forming tubes in the drug delivery segment, each tube having a diameter and a length that extends radially from the inside surface of the drug delivery segment to the outside surface of the drug delivery segment, and where a ratio of the length of the tubes to the diameter of the tubes is about 5–25;

providing a therapeutic drug to the drug delivery segment for more than 24 hours from a catheter; and

distributing the therapeutic drug to a tumor within a patient in approximately equal amounts through the tubes defined in the drug delivery segment.

7. The method of claim 1 wherein the outside surface of the drug delivery segment is substantially annularly grooveless.

8. The method of claim 2 wherein the outside surface of the drug delivery segment is substantially annularly grooveless.

9. The method of claim 3 wherein the outside surface of the drug delivery segment is substantially annularly grooveless.

10. The method of claim 4 wherein the outside surface of the drug delivery segment is substantially annularly grooveless.

11. The method of claim 5 wherein the outside surface of the drug delivery segment is substantially annularly grooveless.

12. The method of claim 6 wherein the outside surface of the drug delivery segment is substantially annularly grooveless.

* * * * *

the catheter **22** joined by connector **50**. This construction provides additional benefits. For example, having the restrictor **90** upstream of the connector **50** acts as a pre-filter, and thus removes any particulates prior to connector **50**. This pre-filter function reduces particulates to the restrictors **70** and **70'** downstream of connector **50**, thus reducing the potential for different pressure drops and flow rates through the restrictors **70** and **70'** downstream of connector **50**, and ultimately the flow rate of the delivered drug through the diffusers or delivery segments **60** at the distal ends. In addition, this embodiment eliminates the possibility for incorrect insertion of a catheter where only one restrictor is downstream of connector, and one restrictor is upstream of connector **50**, and one leg **80** or **80'** not having a restrictor.

FIG. **5B** shows the same structure as FIG. **4B**, except that in this other embodiment of the present invention, a restrictor **90** is placed between proximal end **24** and the first connector **50** downstream of proximal end **24**, to deliver a drug to more than two targeted patient sites.

In accordance with the embodiments shown in FIGS. **4A**, **4B**, **5A**, and **5B**, the drug fluid is pushing through many small pores of the drug delivery segment **60**, and restrictors **70**, **70'** and **90** are of substantially equal flow resistance, and thus the delivered drug fluid follows a tortuous path. In these embodiments, the sum of the resistance to flow through multiple catheter distal ends is preferably equal so that equal flow is through the multiple catheter distal ends is obtained. The structures described above and shown in FIGS. **4A**, **4B**, **5A**, and **5B** provide substantially equal flow through multiple catheter distal ends. Further discussion about the drug delivery segment (i.e. diffuser) and the fluid restrictor is set forth below.

Fluid Diffuser—Fluid modeling reveals that distribution of fluid flow will occur with multiple small holes in simple silicone or polyurethane catheters. The diffuser, i.e., the drug delivery segment **60** shown in FIGS. **4A**, **4B**, **5A** and **5B**, can comprise any suitable structure. For example, the diffuser can comprise material having laser drilled holes or tubes having 0.001–0.005 inches (i.e., 0.0025–0.0127 cm) diameter, and about 20–100 holes per diffuser. In one embodiment, the most distal of forty holes having 0.005 inches (0.0127 cm) in diameter should have 76% of the flow compared to the most proximal hole (total flow 1 microliters/minute). For holes that are 0.001 inches (0.0025 cm) in diameter, the distal hole should have 99.95% of the flow compared to the proximal hole. In addition, many porous materials such as sintered metal, sintered polyethylene, or porous PTFE (i.e., Teflon) have diffuser capability. Thus, these structures are good diffusers at flow rates of about 1 microliter/minute to about 20 microliters/minute. For the diffuser material, a permeability constant of less than about 30,000 and a bubble point of less than about 10 psi is preferred.

As previously noted, the drug delivery segment can be made of any light-weight, high tensile strength material, e.g., tungsten, titanium or tantalum. Further, the drug delivery segment can be made of any suitable radiopaque material (e.g., tantalum, tungsten, titanium, gold, platinum, iridium, silver, nickel, and alloys thereof).

Suitable radiopaque material can be placed in any suitable portion of the medical catheter of the present invention, and is not limited to the drug delivery segment. Thus, the medical catheter of the present invention may include at least one portion comprising a radiopaque material from the group consisting of tantalum, tungsten, titanium, gold, platinum, iridium, silver, nickel and alloys thereof. Incoporation of a portion or marker, such as a band or bead, having radiopaque material can enable medical personnel to identify the location of the cathether and drug delivery segment within a patient, via X-ray, magnetic resonance imaging (MRI), and/or computerized axial tomography (CAT scan).

FIG. **6** is a cross section view of one preferred embodiment of a drug delivery segment (i.e. diffuser) **60** of the present invention taken from lumen distal end **39** of lumen **38** as shown in FIG. **7**. The drug delivery segment is implantable in a patient for long periods of time (i.e., exceeding more than 24 hours), and is particularly useful for implantable drug delivery devices and systems to treat chronic disorders. The drug delivery segment described herein prevents soft tissue from entering the tubes and blocking flow of the fluid from the drug delivery segment to the target site within a patient. The drug delivery segment **60** has an inside surface **120** and an outside surface **130**. In preferred embodiment, drug delivery segment has a longitudinal length of about 0.1–1.0 cm, and more preferably about 0.5 cm. In a preferred embodiment, the inside diameter of diffuser **60** is about 0.032 inches (0.0812 cm), and the outside diameter of diffuser **60** is about 0.064 inches (0.1625 cm). In this preferred embodiment, tubes **101** through **110** extend radially from the inside diameter of diffuser **60** to the outside diameter of diffuser **60**. In this embodiment, the length of the tubes **101** through **110** is about 0.016 inches (0.0406 cm). Preferably, the ratio of tube length to tube diameter of tubes **101** through **110** is about 5–25, and more preferably about 5.0. A benefit of the ratio of 5–25 of tube length to tube diameter is that flow resistance is provided, thereby permitting more equal flow between the most distal tube and the most proximal tube and thus assisting in the diffuser function. One way to obtain this tube structure is to use a laser or ion beam to drill tubes **101** through **110**. In one preferred embodiment, tubes **101** through **110** have substantially the same diameter.

As shown in FIG. **6**, tubes **110** can be tapered as they extend from the outside diameter of diffuser **60** to the inside diameter of diffuser **60**. Lumen **38** extends along the longitudinal axis of Q-Q of diffuser **60**. In a preferred embodiment, all of the tubes **101** through **110** (shown in FIG. **7**) have the same shape as they extend from the outside diameter of diffuser **60** to the inside diameter of diffuser **60**. While tubes **110** are shown as being tapered in FIG. **6**, they can also be non-tapered, or can have tapered and non-tapered sections.

As previously described in connection with FIG. **3B**, the opening defined by the distal end of the medical catheter can be a side opening. When the opening defined by the distal end of the catheter is a side opening, the drug delivery segment can cover the opening. In this alternative embodiment, the drug delivery segment does not define a lumen along its longitudinal axis, but still has tubes that extend radially from the outside surface of the drug delivery segment to the inside surface of the drug delivery segment, wherein the ratio of the length of the tubes to the diameter of the tubes is about 5–25. Further, any pattern of tubes can be used in connection with the present invention, including but not limited to, a pattern corresponding to the shape and/or location of an intended target site within a patient, e.g., a tumor.

FIG. **7** is a side view of one preferred embodiment of the drug delivery segment (i.e. diffuser) **60** of the present invention. In a preferred embodiment, the diffuser **60** comprises at least one row **100** parallel to the longitudinal axis Q-Q of diffuser **60**. In the embodiment shown in FIG. **7**, there are four rows **100** of tubes **101** through **110** extending along an axis parallel to the longitudinal axis Q-Q of

diff-user **60**. In this preferred embodiment, there are ten tubes per row **100**. Preferably, the tubes in each row are equally spaced from each adjacent tube in the same row **100**. As shown in FIG. **7**, tube **101** is the most proximal hole, and tube **110** is the most distal tube, and tube **105** is the middle-tube. As shown in FIGS. **6** and **7**, each row is about 90 degrees from each adjacent row along the outside diameter of diffuser **60** (as FIG. **7** is a side view, only three rows **100** of tubes **101** through **110** are shown). In FIG. **7**, the distance from the most proximal tube **101** to the most distal tube **110** is identified as distance "a", and the distance from the middle tube **105** to about the mid-point of catheter tip **34** is identified as distance "b". In a preferred embodiment, the distance from the most proximal tube **101** to the most distal tube **110** is about 5.5 millimeters, and the distance from middle-tube **105** to about the mid-point of catheter tip **34** is about 5.0 millimeters.

Those of skill in the art will recognize that the above preferred embodiment can be modified without departing from the scope of the present invention. For example, eight (8) rows can be used instead of four (4) rows, wherein each row is about 45 degrees from each adjacent row along the outside surface **130** of the drug delivery segment **60**. Each of the eight rows can have ten (10) tubes **101** through **110**, for a total of eighty (80) tubes.

The key factors in obtaining relatively equal flow through each of the tubes **101** through **110**, are as follows: (1) tube length relative to tube diameter; (2) number of tubes; and (3) an internal diameter of the diffuser **60** that is relatively large enough to provide fluid to the most distal tube **110**. Those of skill in the art will readily recognize how to vary these factors as may be desired for a given flow rate.

The above described embodiment is particularly useful for implantable medical catheters wherein the drug delivery segment is implantable for more than twenty-four hours to provide fluid containing a therapeutic drug to a target site in a patient at flow rates of about 2 microliters/hour to 10 microliters/minute.

Fluid Restrictor—To balance the flow into each hemisphere of the patient's brain, resistance to fluid flow in each leg of the catheter must be significant compared to the resistance at the tissue interface. If the restrictor creates a pressure drop of about 2–10 psi for a flow rate of about 10 microliters/minute, variation in interstitial pressure (less than 0.5 psi) will not create an imbalance of flow in the two catheter legs for a desired flow rate of about 1–10 microliters/minute. For this pressure drop, the material for the restrictor must be very tortuous and have a significant length (i.e., thickness). For the restrictor material, a permeability constant of less than about 5,000 and a bubble point of less than about 10 psi is preferred. Since the restrictor is separated from the diffuser in this embodiment, the dimensions and materials are not limited to those typically considered acceptable for intraparenchymal implant. Acceptable materials for restrictors given the larger lengths possible outside the brain are sintered porous metals, and sintered and/or porous polymers. Methods of manufacture and materials for the restrictors of the present invention include, but are not limited to, thin sheet filter (e.g., polyethersulfone or polypropylene, from Pall Corporation (East Hills, N.Y.)), polycarbonate membrane (from Osmonics, Inc. (Minnetonka, Minn.)), polyvinylidine fluoride from Millipore Corporation (Bedford, Mass.)), depth filters from sintered metal (from Mott, Inc. (Farmington, Conn.)), sintered polyethylene (from Porex Surgical (College Park)), sintered glass (from Robu Glasfilter-Gerate GmbH (Hattert, Germany)), orifice sapphire, and/or capillary tubes. Preferably, the restrictor is a depth filter since it does not have disadvantages that the other materials may have. Sheet membranes have a disadvantage in that they have very small pores that may be prone to clogging and require a high pressure to pass air through the wet membrane (i.e., bubble point). Orifice-type restrictors have the disadvantage of pressure drop that is extremely sensitive to diameter, thereby making it difficult and expensive to match two restrictors of this type to achieve substantially equal flow.

The restrictor should provide a large pressure drop. The pressure drop can be expressed by Darcy's Law. Darcy's Law is as follows:

$$K = \frac{-F\mu T}{A \cdot \text{delta P}}$$

where K=permeability constant
F=flow rate
μ=viscosity for the fluid
T=thickness of porous path
A=surface area
delta P=pressure delta

The conflicting requirements of the large surface area for a diffuser and a large pressure drop for the restrictor can be met by having separate structure for each of these functions.

Separating the restrictors from the diffusers, and placing the restrictors up stream of the diffusers results in the resistance to flow at the distal ends to be insignificant to the overall resistance to flow, and the fluid flow through multiple catheters is substantially equal.

An example is that for a "Y" catheter, if the resistance to flow through a first diffuser has a relative value of 1, and the resistance to flow through a second diffuser has a relative value of 2, then twice as much flow will go through the first diffuser.

On the other hand, if restrictors with a relative resistance value of 100 are placed up stream of the first and second diffusers, so that the overall resistance to flow through the first diffuser has a relative value of 101, and the overall resistance to flow through a second diffuser has a relative value of 102, then the flow through the first and second diffusers will be substantially equal. Equal restriction of fluid flow through each leg is the key to substantially equal fluid flow through each leg.

The features provided by this embodiment include:

1. Separate diffuser and restrictor features for bilateral intraparenchymal drug delivery catheter.
2. Use of simple diffusers that have insufficient tortuosity of the porous structure to make acceptable restrictors.
3. Use of multiple small holes (less than 0.005 inches in diameter; created with a laser) as a fluid diffuser.
4. Location of catheter restrictor at proximal end (not distal) of catheter to provide greater device flexibility, i.e., reduce the number of joint, bonds, components for distal catheter segment.
5. Capability to control flow in the brain catheter with changes in catheter design/materials not directly implanted in the brain tissues.

Thus, the present invention provides for multiple catheter ends for drug delivery. More specifically, the present invention provides for multiple catheter ends, e.g. at least two, into the brain of patient, and even more specifically, into the two different hemispheres of the brain, with each catheter end supplied with therapeutic drugs by the same pump, and with the fluid flow of the therapeutic agent being substantially equal between the two catheter ends.

The present invention also provides a catheter to diffuse a therapeutic agent over a large surface area than from a single point source. The benefits of this structure is that it decreases the fluid flux and reduces the change of damaging patient tissue. In order for equal or near equal bilateral drug

delivery to occur, two catheters are required. It is usually desirable to have equal flow in both catheters to deliver equal amounts of drug to both brain hemispheres.

The present invention can be used for many drug delivery applications, including but not limited to intraparenchymal tissue delivery, intrathecal drug delivery, and intra-cerebral ventricular (ICV) drug delivery.

Many modifications and variations may be made in the techniques and structures described and illustrated herein without departing from the spirit and scope of the present invention. For example, the present invention can be used to infuse a cytostatic agent into a malignant mass located in a variety of places in the body, or infuse a nerve growth factor into the intrathecal space of the spinal column, or to treat Alzheimer's disease by infusing indomethacin or other drug into a patient's hippocampus. Accordingly, the techniques and structures described and illustrated herein should be understood to be illustrative only and not limiting upon the scope of the present invention.

We claim:

1. A method for delivering a therapeutic drug comprising:

forming a drug delivery segment having a longitudinal axis, the drug delivery segment having an outside surface and an inside surface,

forming tubes in the drug delivery segment, each tube having a diameter and a length that extends radially from the inside surface of the drug delivery segment to the outside surface of the drug delivery segment, and where a ratio of the length of the tubes to the diameter of the tubes is about 5–25;

providing a therapeutic drug to the drug delivery segment for more than 24 hours from an intraparenchymal catheter; and

distributing the therapeutic drug in approximately equal amounts through the tubes defined in the drug delivery segment.

2. A method for delivering a therapeutic drug comprising:

forming a drug delivery segment having a longitudinal axis, the drug delivery segment having an outside surface and an inside surface,

forming tubes in the drug delivery segment, each tube having a diameter and a length that extends radially from the inside surface of the drug delivery segment to the outside surface of the drug delivery segment, and where a ratio of the length of the tubes to the diameter of the tubes is about 5–25;

providing a therapeutic drug to the drug delivery segment for more than 24 hours; and distributing the therapeutic drug in approximately equal amounts through the tubes defined in the drug delivery segment to the brain of a patient.

3. A method for delivering a therapeutic drug comprising:

forming a drug delivery segment having a longitudinal axis, the drug delivery segment having an outside surface and an inside surface,

forming tubes in the drug delivery segment, each tube having a diameter and a length that extends radially from the inside surface of the drug delivery segment to the outside surface of the drug delivery segment, and where a ratio of the length of the tubes to the diameter of the tubes is about 5–25;

providing a therapeutic drug to the drug delivery segment for more than 24 hours from an intrathecal catheter; and

distributing the therapeutic drug in approximately equal amounts through the tubes defined in the drug delivery segment.

4. A method for delivering a therapeutic drug comprising:

forming a drug delivery segment having a longitudinal axis, the drug delivery segment having an outside surface and an inside surface,

forming tubes in the drug delivery segment, each tube having a diameter and a length that extends radially from the inside surface of the drug delivery segment to the outside surface of the drug delivery segment, and where a ratio of the length of the tubes to the diameter of the tubes is about 5–25;

providing a therapeutic drug to the drug delivery segment for more than 24 hours from an intracerebral ventricular catheter; and

distributing the therapeutic drug in approximately equal amounts through the tubes defined in the drug delivery segment.

5. A method for delivering a therapeutic drug comprising:

forming a drug delivery segment having a longitudinal axis, the drug delivery segment having an outside surface and an inside surface,

forming tubes in the drug delivery segment, each tube having a diameter and a length that extends radially from the inside surface of the drug delivery segment to the outside surface of the drug delivery segment, and where a ratio of the length of the tubes to the diameter of the tubes is about 5–25;

providing a therapeutic drug to the drug delivery segment for more than 24 hours from a catheter; and

distributing the therapeutic drug into a liquid filled space within a patient in approximately equal amounts through the tubes defined in the drug delivery segment.

6. A method for delivering a therapeutic drug comprising:

forming a drug delivery segment having a longitudinal axis, the drug delivery segment having an outside surface and an inside surface,

forming tubes in the drug delivery segment, each tube having a diameter and a length that extends radially from the inside surface of the drug delivery segment to the outside surface of the drug delivery segment, and where a ratio of the length of the tubes to the diameter of the tubes is about 5–25;

providing a therapeutic drug to the drug delivery segment for more than 24 hours from a catheter; and

distributing the therapeutic drug to a tumor within a patient in approximately equal amounts through the tubes defined in the drug delivery segment.

7. The method of claim 1 wherein the outside surface of the drug delivery segment is substantially annularly grooveless.

8. The method of claim 2 wherein the outside surface of the drug delivery segment is substantially annularly grooveless.

9. The method of claim 3 wherein the outside surface of the drug delivery segment is substantially annularly grooveless.

10. The method of claim 4 wherein the outside surface of the drug delivery segment is substantially annularly grooveless.

11. The method of claim 5 wherein the outside surface of the drug delivery segment is substantially annularly grooveless.

12. The method of claim 6 wherein the outside surface of the drug delivery segment is substantially annularly grooveless.

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